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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/912,674 | 07/20/2001 | Donald S. Karanewsky | 480140.444C1 | 6380 |

500 7590 07/06/2005

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| EXAMINER | |
|---|---|
| LUKTON, DAVID | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1654 | |

DATE MAILED: 07/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/912,674 | KARANEWSKY, DONALD S. | |
| | Examiner | Art Unit | |
| | David Lukton | 1654 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *24 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *1-41 and 43-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicants' election of Group II (claims 41-44) is acknowledged, as are the elected species ((a) the compound of example 190, page 110, and (b) adult RDS as the disease to be treated).

Claims 1-40 and 45-50 are withdrawn from consideration pursuant to the restriction; claims 41, 43 and 44 are withdrawn since they do not encompass the elected disease.

✦

The specification is objected to. Pursuant to the preliminary amendment filed 7/20/01, the first page of the specification was amended to recite that PCT/US99/24756 "claims priority" to application 09/177546. However, the relationship between the PCT application and the prior US application should be specified, i.e., continuation, or else continuation-in-part.

The specification is also objected to because no abstract has been received. (If applicants believe that they submitted an abstract, it is suggested that it be resubmitted).

✦

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 42 is rejected under 35 U.S.C. §112, first paragraph, as containing

subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants have shown (table 3, pages 63-65) that the claimed compounds can inhibit one or more caspases. Based on this, applicants are asserting the claimed compounds can be used to treat any of several diseases including (page 31, line 17+; page 32., line 3+) the following: septic shock, septicemia, and adult respiratory distress syndrome, rheumatoid arthritis, SLE, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, insulin-dependent diabetes mellitus, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, Alzheimer's disease, Parkinson's disease, primary lateral sclerosis, myocardial infarction, stroke, ischemic kidney disease, multiple sclerosis, and amyotrophic lateral sclerosis.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims.

Consider the following:

- Frost Robert A. (*American Journal of Physiology. Regulatory, Integrative and Comparative Physiology* **283** (3) R698-709, 2002) investigated the regulation of TNFα and IL-6 by lipopolysaccharide (LPS) in C2C12 myoblasts and mouse skeletal muscle. Treatment of myocytes with IL-1 or TNF-alpha also increased IL-6 mRNA content, and the increase in IL-6 mRNA due to LPS could not be prevented by pretreatment with antagonists to either IL -1 or TNF. Thus, even if applicants could successfully block all interleukin-1 production using the claimed compounds, interleukin-6 levels could not be controlled, thereby leading to "unpredictable" results on inflammatory response.

- Meyers K. P. (*Inflammation* **17** (2) 121-34, 1993) discloses that interleukin-1 receptor antagonist was not active as an anti-inflammatory agent in the 24-h pleurisy model (carageenan-induced pleurisy).

- Rosenbaum J. T. (*Archives of Ophthalmology* **110** (4) 547-9, 1992) discloses that interleukin-1 receptor antagonist did not produce significant reduction in inflammation subsequent to an active Arthus reaction or subsequent to the intravitreal injection of 125 ng of endotoxin. Rosenbaum suggests that the failure of IL-1RA to be therapeutically effective may be due in part to the presence of other pro-inflammatory cytokines.

- Brennan (*Clinical and Experimental Immunology* **81**, 278-85, 1990) discloses that TGF-β was effective to inhibit IL-1β production in LPs-stimulated peripheral blood mononuclear cells, but only if the cells were pretreated with TGF-β. The IL-1β production was not inhibited if the TGF-β was applied after the inducing stimulus. The point here is that if a scientist has evidence that a given agent "X" is effective to inhibit production of IL-1β when used <u>prior</u> to stimulation of cells (which stimulation produces the IL-1β), attempting to inhibit production of IL-1β by using agent "X" <u>after</u> stimulation of the cells leads to "unpredictable" results.

- Paris (*Journal of Infectious Diseases* **171**, 161-69, 1995) discloses that IL-1RA was not effective to treat inflammation caused by gram-negative bacteria.

With respect to treatment of ischemia and stroke, Read S. J. (*Drugs and Aging* 14 (1) 11-39, 1999) discloses (e.g., abstract) that although many drugs are effective in animal models of cerebral ischemia, these drugs have largely failed to fulfill their promise in clinical trials. Jonas (*Annals NY Acad Sci* 939, 257-67, 2001) discloses that, to the extent that therapeutic efficacy has been achieved in the treatment of ischemia, success could only be achieved if the drug in question was administered within three hours of the ischemic event. The instant claims encompass administration of the compound several days after the ischemia has occurred.

Thus, attempting to extrapolate from *in vitro* ICE inhibition to treatment of inflammatory disease leads to "unpredictable" results; undue experimentation would be required to practice the claimed invention.

✧

Claim 42 is rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Claim 42 is dependent on a non-elected claim.
- Claim 42 is indefinite as to the intended diseases.

✧

The following is a quotation of the appropriate paragraphs of 35 U.S.C. ∋102 that form the basis for the rejections under this section made in this action.

A person shall be entitled to a patent unless -

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 42 is rejected under 35 U.S.C. §102(b) as being anticipated by Dolle (USP 5,585,357).

Dolle discloses (col 19, line 27+) the compound of example 64. This compound is encompassed by instant claim 1 when the substituent variables correspond as follows:

$R^1$ = naphthyl
X = - $CH_2$ -
n = 0
A = valine
$R^2$ = hydrogen
$R^3$ = hydrogen
B = $-CH_2-Z-R^{16}$
Z = -O-
$R^{16}$ = heteroaryl

Also disclosed (col 7, line 61) is that various inflammatory and autoimmune diseases can be treated. Thus, the claim is anticipated.

✦

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, can be reached at (571)272-0974. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

DAVID LUKTON
PATENT EXAMINER
GROUP 1600